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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/963,927	09/26/2001	Thomas Rogers	3391/PCT	1278

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/963,927	ROGERS ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 4 is/are allowed.

6)☒ Claim(s) *1-3 and 5-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 4/5/05, claims 1-7 have been amended, and claims 8-16 added. Claims 1-16 are now pending.

Applicants' arguments filed 7/29/04 have been considered and found persuasive in part. The rejection of claim 5 under 35 USC §101 is withdrawn.

The rejection of claim 1 as anticipated by Ruminski (WO 97/08145) is withdrawn.

✦

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 now recites the following:

"the compound corresponds in structure to formula I"

It does not appear that there is descriptive support for this language. Applicants are requested to point to the page and line number where support can be found.

✦

Claims 5-16 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, the claims which recite or imply therapeutic efficacy are not enabled. It is stated (page 74, line 6+, specification) that some of the claimed compounds exhibit an IC_{50} of 0.1 nM to 100 micromolar in the "293-cell" assay. Presumably the term "293-cell" is referring (page 78, line 29+) to 293 embryonic kidney cells. However, this does not mean that there exists a human disease which can be successfully treated using the claimed compounds.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

The specification asserts (p 6, line 16+ ; p. 20, line 10) that various diseases can be successfully treated using the claimed compounds. However, in attempting to extrapolate from *in vitro* results to treatment of ill patients, "unpredictable" results are obtained.

Consider, for example, the following:

- Nicosia (*American Journal of Pathology* 138 (4) 829-33, 1991) discloses that the peptide GRGDS is effective to inhibit angiogenesis, but that if the aspartic acid side chain is extended by just one methylene group, loss of activity results. Thus, the conclusion is that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned.

- Belo (*Inflammation* 25 (2) 91-6, 2001) discloses that thalidomide inhibited angiogenesis in mice, but failed to inhibit tumor growth in the same mouse strain.

- Mundhenke, "Tissue examination to monitor antiangiogenic therapy: a phase I clinical trial with endostatin" (*Clinical Cancer Research* 7 (11) 3366-74, 2001) disclosed the results of a phase I clinical trial with endostatin, which is an angiogenesis inhibitor. The result is that the endostatin was not particularly effective in treating cancer patients.

- Boehm-Viswanathan (*International Journal of Molecular Medicine* 4 (4) 413-7, 1999) suggests that inhibition of angiogenesis offers the potential to effectively treat patients afflicted with cancer, but that so far success in humans has proven elusive.

- Pignatelli (*Human Pathology* 23 (10) 1159-66, 1992) discloses that in breast carcinomas, expression of integrins is downregulated. This tends to suggest that if one makes "static" assumptions about the level of expression of integrins on tumor cells, an "unpredictable" outcome is likely.

Thus, the skilled artisan would have concluded from the foregoing references that when when inhibition of angiogenesis can be achieved by a given compound "Z", success in the reduction of tumor volumes by the compound "Z" in vivo is "unpredictable". The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* 15 (3) 367-73, 1996); Kemeny (*Seminars in Oncology* 21 (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* 9 (12) 2815-29, 2000);

Giese (*Journal of Cancer Research and Clinical Oncology* 127 (4) 217-25, 2001); Garattini (*European Journal of Cancer* 37 Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* 40 (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited in vitro activity leads to "unpredictable" results. Thus, while offering hope for the future, the reference (Boehm-Viswanathan) nevertheless indicates that at the time of the invention, administration of angiogenesis inhibitors to humans suffering from cancer would have produced "unpredictable" results.

But suppose, at some point in the future, applicants could show that one specific form of cancer could be successfully treated by the claimed compounds. It would not follow that all forms of cancer could be successfully treated using the claimed compounds. The term "cancer" or "tumor" encompasses a wide variety of proliferative diseases, such as the following: prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, melanomas of the skin, cancer of the Kidney and Renal Pelvis, pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, testicular cancer, intestinal cancer, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum, gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer,

pancreatic cancer, kidney cancer (renal cell), prostate cancer, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma. Many, if not most of these would qualify as "solid tumors". There is no evidence of record that there exists any one agent that is effective against all of these cancer types, or most of them. The skilled oncologist would not regard it as realistic that one can extrapolate from a showing of inhibition of growth of one cancer cell type to inhibition of growth of <u>all</u> cancer cell types, even all solid tumor types. Given that there is not evidence that even one specific solid tumor can be successfully

treated, and the fact that there isn't even a description of specific tumor types that can be successfully treated, it is suggested that the phrase "solid tumor growth" and "metastasis" be deleted from claim 7, and excluded from claims 5 and 6. (Claims 5-7 would remain rejected, however, even if such an amendment were introduced).

With respect to the matter of inflammatory diseases, consider the following reference:

> Theien B. E. (*Journal of Clinical Investigation* 107 (8) 995-1006, 2001) compared the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS.

Accordingly, one cannot predict success in the treatment of inflammation based on the propensity of a compound to antagonize integrins.

On the subject of restenosis, applicants have provided no evidence that the claimed compounds will be effective to treat this disorder. Nor has any evidence been provided that, at the time of the invention, it was well known in the art that antagonists of the $\alpha_v\beta_3$ integrin will be effective in this regard. Consider the following, which pertain to restenosis:

- Gibson C. M. (*Journal of the American College of Cardiology* 32 (1) 28-34, 1998)

investigated the effects of tirofiban versus placebo on the incidence of adverse cardiac outcomes and coronary artery restenosis at 6 months. Gibson found a beneficial effect at a period seven days post- angioplasty, but after 6 months, the benefit ceased to be statistically significant.

- Huckle W. R. (*Circulation* 103 (14) 1899-905, 2001) studied the effects of the endothelin antagonist L-749,329 in an animal model of angioplasty. Huckle discloses that after 28 days of administration, mean neointimal thickness in the L-749,329-treated group was reduced by 9.0% compared with vehicle-treated controls, but that this effect was not statistically significant (P=0.13).

- Veinot J P (*Canadian Journal of Cardiology* 12 (1) 65-70, 1996) undertook a study on the efficacy of the HMGCoA reductase inhibitor lovastatin as a therapeutic agent for coronary arterial restenosis post-balloon angioplasty. The amounts of arterial injury and neointimal thickening were quantitated. A series of linear regression models was used to control for the degree of injury. It was found that the reduction of neointimal thickness for the lovastatin group compared with the control animals was 0.08 mm, a statistically significant result ($P < 0.05$). At the same time, however, the authors concluded that although lovastatin produced a statistically significant decrease in neointimal thickness post-balloon angioplasty, when extrapolated to angiographical end-points, the differences would not be clinically significant. These data suggest that lovastatin may be of marginal use in humans for limiting restenosis .

Thus, in view of the foregoing (Gibson, Huckle, Veinot), the physiological changes following an attempted therapy of restenosis may appear on the surface to be "beneficial", but on closer inspection may actually be of no significance statistically; or perhaps the physiological changes will be statistically significant at one point in time, only to become statistically insignificant at a later time; or the observed physiological changes may be statistically significant, but not "predictive" of therapeutic efficacy.

Claim 6 (and 7) is rejected for each of two separate reasons: (a) this claim recites the term

"therapeutically effective", and (b) this claim recites the term "inhibiting a condition". "Inhibition of a condition" constitutes ambiguous language, and language which is not generally used by medical practitioners. However, if one endeavors to "inhibit" a disease, one is endeavoring to mitigate the symptoms resulting from that disease. For example, if a person were to endeavor to "inhibit" a headache, he might take aspirin. If a person were endeavoring to "inhibit" hypertension, he might take an ACE inhibitor. Thus, inhibition of a condition is such as to encompass "treatment" of the condition; accordingly rejection of this claim for lack of enablement is justified.

In response to the foregoing, applicants have made several arguments beginning with the statement that they have asserted therapeutic efficacy. Applicants have gone on to imply that if an applicant asserts therapeutic efficacy, this is an adequate substitute for evidence of the same. However, applicants are not correct on this point. Applicants have also argued that they have suggested assays that could be used to determine whether or not the compounds can be used therapeutically. However, this does not amount of a showing of "how to use" the compounds. Applicants have also stated that they have explained how to make the compounds. This is true; however, the examiner has never argued that "undue experimentation" would be required to synthesize any one of the compounds.

Next, applicants have attempted to address the examiner's arguments regarding "unpredictability". In response to Nicosia (*American Journal of Pathology* 138 (4)

829-33, 1991), applicants have argued that this reference does not support the assertion of unpredictability, at least when the issue is that of extrapolation from the test tube or Petri dish to the intact animal. Perhaps this would seem to be true on the surface. However, the issue is not quite as simple as applicants are making it. One of the points here is that there is a spectrum of inhibitory potencies, ranging from very effective to totally ineffective. Applicants would probably like to argue that there is in fact no such "spectrum" of activities, and that a compound is either highly effective or totally ineffective. As agreed by examiner and applicants, Nicosia provides an example of a "first" compound which inhibits angiogenesis, and a second compound which does not. However, the skilled artisan would recognize that there is a spectrum of possibilities with regard to efficacy. Perhaps it is true that Nicosia taken by itself does not prove that the claimed invention will fail. However, in the event that applicants choose to point to an example of a compound falling outside the scope of the claimed invention which is effective to treat a specific type of tumor, Nicosia will come into play. This is because of, again, the principle of degrees of efficacy, and the inability of the skilled artisan to predict the degree of efficacy that a compound will exhibit. Applicants may choose to point to an example of a compound falling outside the scope of the claimed invention which is effective to treat a specific type of tumor; that compound might be twice as effective as any of those claimed, or perhaps it will be 10 times as effective, or 100 times as effective. If the compound

which applicants may choose to point to is 10 times as effective as any that is claimed, then one cannot in fact predict therapeutic efficacy of the claimed compounds. Thus, in comparing anti-tumor compounds with the claimed compounds, Nicosia will indeed come into play.

Next, applicants have questioned the effectiveness of Mundhenke (*Clinical Cancer Research* 7 (11) 3366-74, 2001) in establishing unpredictability. Applicants have argued that the experiments disclosed in the reference were not intended to test endostatin efficacy. What applicants appear to be arguing is that the behavior of compounds in *in vivo* assays is determined by the hopes and wishes of those observing the experiments, rather than by the laws of chemistry and physics. However, this is not true. Suppose that there are two rats, each implanted with a tumor. The "first" scientist administers an anti-angiogenesis compound to the "first" rat, and the "second" scientist administers the same compound to the "second" rat. The conditions of the two experiments are identical. The only difference is that, for one reason or another, the "second" scientist is hoping that the compound will not be effective, whereas the first scientist is hoping that the compound will be effective. Is it applicants position that the first rat will exhibit signs of reduced tumor growth, while at the same time the tumor in the second rat will be unaffected by the compound, or is it applicants view that the laws of chemistry and physics will prevail?

Applicants have also argued, with respect to claims 5, 6, 8-11 and 13, that they should not

be required to list all of the diseases that one might be able to treat using the claimed compounds. Essentially applicants are arguing that it is up to others to determine which diseases are mediated by $\alpha_v \beta_3$ or $\alpha_v \beta_5$, then to determine which are the diseases for which antagonism of $\alpha_v\beta_3$ or $\alpha_v\beta_5$ could potentially produce a therapeutic effect, and then to determine whether in fact the symptoms of the disease in question can actually be ameliorated by one of the claimed compounds. This argument is found to be unpersuasive. Even apart from the issue of unpredictability, there is the matter of "guidance", as referred to in *Forman* and in *Wands*. If applicants are not even willing to assert a list of diseases that they hope can be successfully treated, guidance is clearly lacking. As for the "breadth" of the claims, those claims that merely reference integrin-mediated conditions are sufficiently broad to encompass most known human diseases. As such, this is another factor weighing against a finding of enablement. Thus, in view of the absence of guidance presented, the absence of working examples that might show the skilled artisan how to treat human (or animal) disease, the state of the prior art, the unpredictability of the art, and breadth of the claims, it is evident that "undue experimentation" would be required to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800